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Preclinical and Clinical Evaluation of Elotuzumab, a SLAMF7-targeted Humanized Monoclonal Antibody in Development for Multiple Myeloma

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Abstract

Although multiple myeloma has historically been treated with chemotherapy, prolonged survival has only been possible since the introduction of thalidomide, lenalidomide and bortezomib. However, multiple myeloma remains largely incurable and new treatments are needed to improve long-term outcome.

Elotuzumab is a humanized IgG1 monoclonal antibody that targets Signaling Lymphocyte Activation Molecule Family member 7 (SLAMF7) to activate natural killer cells, enabling selective killing of myeloma cells with minimal effects on normal tissue. The combination of elotuzumab with anti-myeloma therapies that stimulate host immunity may be an attractive treatment option for patients with newly diagnosed or relapsed/refractory multiple myeloma. Here we review the role of SLAMF7 in the pathogenesis of multiple myeloma and the preclinical and clinical development of elotuzumab.

Introduction

Multiple myeloma is a neoplasm that results in the accumulation of monoclonal plasma cells, predominantly in the bone marrow, which interfere with the production of normal white blood cells, red blood cells and platelets [1]. It is the second most common hematological cancer after lymphoma [1], with an estimated incidence rate of 8 per 100,000 people and an estimated mortality rate of 2.2 per 100,000 people in Europe in 2012 [2]. Multiple myeloma remains largely incurable using current treatment approaches with fewer than 50% of patients surviving five years after diagnosis [3].

Treatment for multiple myeloma depends on the type and stage of disease, as well as the patient's general health. Melphalan, a nitrogen mustard alkylating agent, administered with prednisone, has been used since the 1960s [4], with the combination of high-dose chemotherapy (HDC) and autologous stem cell therapy (ASCT) introduced in the 1980s [5]. However, long-term survival with these approaches is rare and most patients who initially respond to treatment eventually relapse [6]. Upon progression, multiple myeloma is a debilitating malignancy characterized by bleeding, infection, bone destruction (including pathological fractures and spinal cord compression), anemia, elevated calcium and renal insufficiency or failure [1].

The introduction of immunomodulatory therapies and proteasome inhibitors such as thalidomide, its amino-substituted analogue lenalidomide, bortezomib [7], carfilzomib and pomalidomide have helped delay the onset of progressive disease. These agents, when used alone or as part of a combination strategy, have all improved survival compared with controls in phase III trials and have consequently been approved for use [8–14] (carfilzomib approved in the US only). Thalidomide is indicated in combination with melphalan and prednisone as a first-line treatment for patients aged 65 years or older, or patients ineligible for HDC [15]. Lenalidomide was approved in combination with dexamethasone for adult patients who have received at least one prior therapy; however, this has recently been expanded to include patients with newly diagnosed MM [16], while bortezomib monotherapy is indicated for patients with relapsed/refractory MM. and in combination with melphalan and prednisone for adult patients with previously untreated multiple myeloma [17]. Carfilzomib (US only) and pomalidomide have also been granted approval in patients who have received at least two prior lines of therapy [18, 19]. Interestingly, recent studies have shown that

treatment with lenalidomide plus conventional chemotherapy significantly reduces the risk of progression in newly diagnosed, young multiple myeloma patients aged <65 years [20], potentially providing an alternative treatment option for a patient group that typically receive HDC plus ASCT as standard. In addition, a meta-analysis of 1435 patients treated across four European phase III trials that included thalidomide and/or bortezomib-containing treatment arms showed that being ≥75 years of age or having renal failure at presentation, and the occurrence of cardiac, infective or gastrointestinal adverse events (AEs) negatively affected survival. This suggests that appropriate screening for vulnerability, assessment of organ function and less-intense treatment approaches should be considered in frail and elderly multiple myeloma patients to improve tolerability and optimize efficacy [21].

Although the introduction of new agents and use of ASCT has improved the overall survival (OS) of patients with multiple myeloma, nearly all patients will experience acquired resistance leading to disease relapse. In addition, patients refractory or intolerant to these agents, such as those ineligible for SCT, have a poor median OS (9–10 months) [22–24].

The development of resistance over the course of treatment is thought to arise from a number of mechanisms. These include the selection and persistence of resistant multiple myeloma cancer cell subclones, cytogenetic and epigenetic alterations and deregulated signaling pathways [25]. Furthermore, a number of immunosuppressive mechanisms in the bone marrow and tumor micro-environment can hamper anti-myeloma immunity approaches by shielding such clones, resulting in relapse or disease progression [25]. Alteration of immune cells, including T cells, B cells, natural killer (NK) cells and dendritic cells, has also been described in multiple myeloma, leading to a loss of tumor immunosurveillance and providing protection to targeted cell death [26, 27].

Ongoing studies have shown promising outcomes with triplet treatment combinations, compared with doublet combinations in terms of progression-free survival (PFS), possibly due to the multiple mechanisms of action that are employed when three agents are administered concurrently. For example, median PFS with carfilzomib in combination with lenalidomide and dexamethasone has been shown to be 26.3 months, compared with 17.6 months in patients treated with lenalidomide and dexamethasone only [28]. Nevertheless, given the heterogeneous nature of the oncogenic processes involved in multiple myeloma and the immunosuppressive mechanisms that play a critical role in

myeloma tumor cell survival and environment-mediated drug resistance [25], there is a further need for a combined treatment modalities approach, which should include an element that effectively targets the immune system [29, 30]. Combined treatment modalities may enable sustained complete responses in a significant number of patients, in particular if therapy is given during the early phases of disease or early relapse, before disease-related immune dysfunction and multiple courses of treatment negatively impact the patient's immune function [31–33]. Furthermore, tolerability of treatment-related toxicities may also be better during early treatment, especially in ASCT-ineligible patients [31].

One approach to developing myeloma-selective therapy has been the investigation of monoclonal antibodies (mAbs) targeting antigens expressed exclusively or predominantly on multiple myeloma cells. Antigens may include those involved in cell survival, antiapoptotic pathways, cell-to-cell communication, angiogenesis and interactions between multiple myeloma cells in the tumor and bone marrow microenvironment. The mechanisms of action of mAbs include both direct tumor cell destruction, and indirect mechanisms such as the regulation of immune responses through complement-dependent cytotoxicity (CDC) and/or antibody-dependent cell-mediated cytotoxicity (ADCC) [34]. Elotuzumab, is a humanized mAb that targets the antigen Signaling Lymphocyte Activation Molecule Family member 7 (SLAMF7), expression of which is largely restricted to neoplastic plasma cells and NK cells as opposed to other, normal tissues. This review focuses on the role of SLAMF7 in the pathogenesis of multiple myeloma and the preclinical and clinical development of elotuzumab, and discusses the role of this mAb in combination with other multiple myeloma therapies.

Preclinical Rationale

SLAMF7 is a glycosylated cell surface protein and a member of the SLAM (signaling lymphocyte activation molecules) family [35]. It was first identified on NK cells, mediating their adhesion and function through a self-ligand binding interaction [36, 37]. Self-engagement of SLAMF7, or engagement by SLAMF7-specific antibodies, leads to association with its adaptor protein (EAT-2),

resulting in enhanced activation of NK cells, promoting their ability to mediate killing of target cells through the subsequent release of cytotoxic granules [37, 38].

Using a subtractive hybridization approach, Hsi and colleagues demonstrated that the SLAMF7 gene was highly expressed in plasma cells [39]. This was confirmed by gene expression profiling that showed high SLAMF7 expression in plasma cells from healthy donors, with lower expression in NK cells and normal non-lymphoid tissues [39]. Importantly, SLAMF7 mRNA was highly expressed across the various molecular subtypes of myeloma, including all cytogenetic risk groups. Indeed, an analysis of bone marrow plasma cells collected from multiple myeloma patients showed that the SLAMF7 protein was expressed in all samples, with 19/20 samples having >75% expression of SLAMF7 [39]. In a separate analysis, low but detectable levels of soluble SLAMF7 (sSLAMF7) were found in the sera of some patients with multiple myeloma, while sSLAMF7 was not present in healthy donor sera [40]. Although there was no correlation between SLAMF7 surface expression and disease stage, patients with advanced stage or symptomatic multiple myeloma (International Stage Systems [ISS] II/III) had significantly higher levels of sSLAMF7 than those with ISS I, suggesting that sSLAMF7 may represent a biomarker of disease progression [40].

SLAMF7 is highly expressed in benign and neoplastic plasma cells, expressed at lower levels on the surface of NK cells, is infrequently expressed in the parenchyma of any major organs and is not found on hematopoietic stem cells [37, 39], making it a unique protein for the therapeutic targeting of multiple myeloma cells. Consequently, the humanized monoclonal immunoglobulin G1 antibody elotuzumab, which targets SLAMF7, was developed.

Mechanism of Action

The primary mechanism of action of elotuzumab is the lysis of multiple myeloma cells via ADCC (Figure 1), a process initially thought to be dependent on the presence of NK cells or other peripheral blood mononuclear cells (PBMCs) [39, 40]. However, as depletion of T cells, B cells or monocytes from a PBMC effector cell population had no effect on elotuzumab-induced ADCC, it was suggested that the lytic activity of elotuzumab is primarily mediated by NK cells [39]. Indeed,

elotuzumab binds to SLAMF7 on multiple myeloma cells, while also binding to CD16 on NK cells, activating NK cells to lyse the antibody-bound tumor cells [41]. It has also been shown that elotuzumab directly activates NK cells by binding to SLAMF7 on their surface and enhances their anti-myeloma activity via interaction with the signaling intermediary EAT-2, which is present in NK cells but absent in primary, human multiple myeloma cells [38, 41]. Interestingly, *in vivo* treatment with elotuzumab resulted in the lysis of multiple myeloma cells from patients who were resistant to conventional therapies [40]. There are other proposed mechanisms by which elotuzumab could target multiple myeloma cells [41–43]. For example, it has been suggested that elotuzumab may impair the adhesion of SLAMF7-expressing multiple myeloma cells to bone marrow stromal cells (BMSCs) [40]. This proposal was supported by *in vitro* studies in which the downregulation of SLAMF7 by a lentiviral short interfering RNA line prevented human multiple myeloma cells from binding to cultured BMSCs [40].

Early Clinical Experience

On the basis of promising preclinical results, elotuzumab was evaluated as monotherapy in a phase I, dose-escalation trial (Table 1) [44–47]. Patients with relapsed or refractory multiple myeloma were treated with intravenous elotuzumab at one of six dose levels (0.5 to 20 mg/kg) once every 14 days for 8 weeks, with the option of a second course of treatment in patients without relapse [44]. Study endpoints included safety, tolerability and pharmacokinetic profile. Elotuzumab was generally well tolerated. Most treatment-related AEs were grade 1 or 2 in severity, with the most common (>10% of patients) including chills, pyrexia and flushing (Table 2) [44–48]. The maximum tolerated dose was not reached. Infusion-related events were observed in 20 (59%) patients although these were mitigated after the protocol was amended to include premedication before the first elotuzumab dose. Although no objective responses were observed, 9/35 (26%) heavily-pretreated patients had stable disease according to the European Group for Blood and Marrow Transplantation myeloma response criteria [44].

Elotuzumab-Based Combination Therapy

Preclinical rationale

The relatively modest antitumor activity of elotuzumab monotherapy may be attributable to immunosuppressive effects. Multiple myeloma cells have a unique ability to elude immunosurveillance due to both dendritic cell and regulatory T cell abnormalities, and the secretion of immunoregulatory cytokines (e.g. by BMSCs) into the tumor microenvironment [49]. In addition, multiple myeloma is associated with decreased NK cell function and an increase in the number of immunosuppressive myeloid-derived suppressor cells in peripheral blood and bone marrow [50, 51].

Due to its distinct mechanism of action, elotuzumab is likely to act synergistically with treatment modalities that stimulate host anti-myeloma immunity; therefore, combination approaches may be more effective than single-agent therapy. For example, combination with lenalidomide or thalidomide may improve clinical benefit as these agents alter cytokine production and enhance T- and NK-cell-mediated immune responses [52, 53]. In addition, as proteasome inhibition stimulates apoptosis, reduces angiogenesis, cytokine signaling and cell adhesion, and can increase the susceptibility of multiple myeloma cells to NK cell-mediated killing [54, 55], combination with bortezomib may also be effective [56, 57]. In preclinical studies, overnight pretreatment of multiple myeloma cells with dexamethasone, bortezomib, lenalidomide or perifosine (an Akt inhibitor) enhanced elotuzumab-induced lysis of multiple myeloma cells (Figure 2) [40]. Furthermore, in a mouse model of multiple myeloma, the combination of elotuzumab with bortezomib significantly increased *in vivo* antitumor activity compared with elotuzumab alone [58].

An alternative strategy could be to combine elotuzumab with mAbs that augment antitumor immune responses through indirect modulation of immune regulatory checkpoints. Possible combination partners include inhibitors of programmed death 1 and cytotoxic T-lymphocyte-associated antigen-4 or CD137 agonists [49, 59–61]. This approach is supported by results from xenograft transplant models of breast cancer, where stimulation of NK cells with agonistic CD137 antibodies enhanced the efficacy of the ADCC-mediating mAb trastuzumab [62]. In addition, immunostimulation with an agonistic CD137 antibody in mouse models of myeloma has been shown to activate NK cells [61].

Many other agents have the potential to enhance clinical benefit when combined with elotuzumab. For example, NK cell-mediated ADCC is enhanced by administration of monoclonal antibodies to inhibitory killer immunoglobulin-like receptors [63]. In addition, compounds that disrupt the immunosuppressive microenvironment, for example by modulating the number or function of T regulatory cells or indoleamine 2,3-dioxygenase expression [64], may also be valuable combination partners.

Clinical experience and ongoing studies

The combination of elotuzumab with bortezomib or with lenalidomide plus low dose dexamethasone has been evaluated in two phase I clinical trials in patients with relapsed or refractory multiple myeloma. Among patients treated with elotuzumab plus bortezomib, the objective response rates (ORRs) were 48% for all evaluable patients ($n = 28$) and 67% for patients refractory to bortezomib (Table 1). The most frequent grade 3 or 4 AEs were lymphopenia (25% of patients) and fatigue (14%) (Table 2; [45]). During the study, the protocol was amended to include patients with no prior bortezomib treatment and those who were responsive (partial response or better) to prior bortezomib treatment for ≥ 3 months, or who were responsive to prior bortezomib treatment at the time of switching to another treatment or ceasing treatment, and excluded patients who had been treated with bortezomib less than 3 months before the initial dose [45].

In a phase IB study of elotuzumab at a dose of 5, 10 or 20 mg/kg with lenalidomide and low-dose dexamethasone, the ORR was 82% ($n = 29$) (Table 1) [46]. For the 20 mg/kg cohort, median time to progression had not been reached after a median follow-up of 16.4 months. Among all patients, the most common grade 3 or 4 treatment-emergent AEs were neutropenia (36%) and thrombocytopenia (21%); 89% of patients experienced at least one infusion reaction, although most of these resolved either spontaneously or with supportive care (Table 2; [46]). Patients who had received prior lenalidomide treatment within the preceding 6 weeks were excluded from the study.

A phase II trial of elotuzumab at a dose of 10 or 20 mg/kg plus lenalidomide (25 mg) and low-dose dexamethasone (40 mg) has recently been completed in 73 patients with relapsed or refractory

multiple myeloma [47]. The primary objective was ORR (\geq partial response per International Myeloma Working Group Criteria), with PFS and safety as key secondary endpoints [47]. The overall ORR was 84%, comprising 92% of patients treated with 10 mg/kg elotuzumab and 76% patients treated with 20 mg/kg elotuzumab (Table 1) [47]. Median PFS was 29 months overall, 32 months and 25 months in the 10 mg/kg and 20 mg/kg cohorts, respectively. The most common treatment-emergent AEs were diarrhea (66%), muscle spasms (62%), fatigue (56%), constipation (51%), nausea (48%), and upper respiratory tract infection (47%). Serious AEs were reported in 58% of patients, most commonly pneumonia (12%).;

The overall rate of infusion reactions at study completion was 11% [47]. The most common infusion reactions were pyrexia and rash, which occurred in 3 patients each [65]. In order to mitigate infusion reactions, patients were premedicated before each elotuzumab infusion. Pretreatment for infusion reactions originally included an antihistamine and acetaminophen, which was optional for patients who experienced any infusion reaction [46]; during the course of the study, the pretreatment regimen evolved considerably, reducing the severity and incidence of infusion reactions [66]. A long-term safety analysis revealed a consistent safety profile following 18 months of therapy versus the safety profile observed within the first 18 months. No new safety signals were identified [48]. Patients within the Phase 2 portion of this study were excluded if they had received prior lenalidomide therapy (prior lenalidomide was permitted in Phase 1). Based on the results of this study to date, the U.S. Food and Drug Administration (FDA) granted elotuzumab Breakthrough Therapy Designation for use in combination with lenalidomide and dexamethasone for the treatment of multiple myeloma in patients who have received one or more prior therapies.

Several other elotuzumab-based trials are currently ongoing or recruiting patients (Table 3) [44, 45, 47, 67–72], the results of which will further enhance the understanding of elotuzumab in multiple myeloma. The Phase 3 ELOQUENT-2 trial (NCT01239797) further investigates elotuzumab in combination with lenalidomide and dexamethasone in relapsed and refractory patients, using a randomized, controlled study design. The Phase 3 ELOQUENT-1 trial (NCT01335399) examines this combination as first-line therapy for multiple myeloma. In addition, further research into the biology of SLAMF7 in normal and multiple myeloma cells, including in PMBCs other than NK cells, is ongoing.

Conclusions and Future Directions

New therapeutic strategies are still required in multiple myeloma to further prolong remission without impacting on safety. Early indications from clinical studies suggest that elotuzumab has promise in multiple myeloma, particularly when used in combination with other anti-myeloma therapies. Elotuzumab, in combination with lenalidomide plus dexamethasone, has been shown to result in a high ORR and extended PFS in patients with relapsed or refractory multiple myeloma with no significant overlapping toxicity reported. Results from the two phase III trials (Table 3) will determine whether or not the combination should be recommended for patients with either newly diagnosed or relapsed/refractory multiple myeloma. Currently, there are no data to support the use of elotuzumab in newly diagnosed patients, although several trials are ongoing in this population. Because expression of SLAMF7 on multiple myeloma cells has been shown to be independent of disease stage, first-line treatment may be effective. In addition, use of immunotherapy earlier in the course of the disease may be more beneficial as immune dysfunction is known to become more prevalent as the disease progresses [73].

With continued development, elotuzumab-based regimens have the potential to become an integral component of the treatment armamentarium for multiple myeloma; providing hope for even better outcomes in the future.

Expert commentary

Multiple myeloma is a debilitating malignancy characterized by a chronic series of relapses until death. Historically, treatment with melphalan plus prednisone or high-dose chemotherapy plus autologous stem cell therapy failed to improve long-term survival and prevent relapse in patients with multiple myeloma. However, in recent years, the availability of novel therapies such as the immunomodulatory drugs thalidomide and lenalidomide, and the proteasome inhibitor bortezomib, has significantly advanced treatment, resulting in improved survival rates and longer remission times. Nevertheless, most patients still struggle to achieve therapeutic goals due to patient characteristics (eg, older age and ineligibility for stem cell transplantation) and treatment-related toxicities, and multiple myeloma remains an incurable disease. Thus, there is an urgent unmet medical need for more effective therapies.

The optimal goals of multiple myeloma therapy are to prolong survival with minimal toxicity while maximizing durability of response and long-lasting symptom relief. To this end, second generation novel agents, such as the immunomodulatory drug pomalidomide, and the proteasome inhibitors carfilzomib and ixazomib, may build upon the efficacy of first generation agents to improve outcomes further. Moreover, as demonstrated by recent and ongoing clinical trials, monoclonal antibodies that activate the immune response and target myeloma cells specifically, such as the anti-SLAMF7 agent elotuzumab, may offer the potential for clinically relevant improvements in outcome in the future, particularly considering their good safety and tolerability profile when administered in combination with other anti-myeloma therapies.

Five-year view

The results of ongoing studies with elotuzumab and other monoclonal antibodies are likely to influence treatment of multiple myeloma over the next 5 years. If the results of pivotal trials are positive, monoclonal antibodies may become the backbone of multiple myeloma treatment in combination with currently available standard therapies, potentially offering improved rates of long-term survival with acceptable tolerability profiles. In the case of elotuzumab in particular, such combinations may also be recommended for patients with newly diagnosed or relapsed/refractory multiple myeloma, exploiting the disease stage independence of SLAMF7 expression on multiple myeloma cells and the benefits of targeting immune dysfunction early in the course of the disease.

The cost of managing multiple myeloma is significant and extends beyond the price of treatment, encompassing the costs associated with disease management and treatment of adverse events. If they are proven to significantly improve remission duration and have favourable safety and tolerability profiles, monoclonal antibodies such as elotuzumab may also offer pharmacoeconomic benefits, although further evidence on the pharmacoeconomic benefits of monoclonal antibodies is still required.

Novel combinations of therapies are another avenue that is likely to be extensively explored in clinical trials over the next 5 years. Combining monoclonal antibodies that target tumour cells directly with monoclonal antibodies that augment antitumor immune responses through indirect modulation of immune regulatory checkpoints is an approach that holds considerable promise. Indeed, inhibitors of

programmed death 1 and cytotoxic T-lymphocyte-associated antigen-4, and agonists of CD137 have already shown encouraging results in several cancers including multiple myeloma. Several other agents also have the potential to enhance clinical benefit when combined with monoclonal antibodies that target tumour cells directly, including monoclonal antibodies against inhibitory killer immunoglobulin-like receptors and agents that disrupt the immunosuppressive microenvironment. Other potential treatment approaches that could be utilized in multiple myeloma to overcome immune deficiencies include therapeutic vaccines [74, 75], and chimeric antigen receptor-expressing T cells [76, 77]; although further investigations are still needed with these agents. Immune dysfunction is a key characteristic of multiple myeloma and, therefore, directly targeting and stimulating the immune system is promising treatment of approach.

Overall, the treatment landscape for multiple myeloma is likely to change significantly over the next five years, providing real hope for better outcomes in patients with this debilitating disease.

Key issues

- With an estimated incidence rate of 8 per 100,000 people, multiple myeloma is the second most common hematological cancer after lymphoma.
- Although historically treated with chemotherapy, the recent approvals of thalidomide, lenalidomide and bortezomib have prolonged survival of patients with multiple myeloma; nevertheless, fewer than 50% of patients survive for five years after diagnosis.
- Therefore, new treatments are urgently required to improve the long-term outlook of such patients, particularly those with relapsed multiple myeloma.
- Elotuzumab is a humanized IgG1 monoclonal antibody that binds to Signaling Lymphocyte Activation Molecule Family member 7 (SLAMF7), a glycoprotein expressed by myeloma and natural killer cells.
- The binding of elotuzumab to SLAMF7 activates natural killer cells, but not myeloma cells. Elotuzumab bound to myeloma cells via SLAMF7 further activates natural killer cells via a CD16 mediated pathway, enabling selective killing of myeloma cells with minimal effects on normal tissue

- Due to its distinct mechanism of action, elotuzumab is likely to act synergistically with treatment modalities that stimulate host anti-myeloma immunity; thus, the combination of elotuzumab with anti-myeloma therapies that stimulate host immunity is an attractive treatment option, especially early in the course of the disease before disease-related immune dysfunction and multiple courses of treatment negatively impact immune function.
- Indeed, the combination of elotuzumab with bortezomib or lenalidomide plus low dose dexamethasone has shown promising activity in two phase I clinical trials in patients with relapsed or refractory multiple myeloma; phase III combination trials in patients with newly diagnosed or relapsed/refractory multiple myeloma are ongoing.
- The results of these trials may support the use of elotuzumab-based treatment regimens in multiple myeloma.

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Figure Legends

Figure 1. Mechanism of action of elotuzumab against multiple myeloma cells.

Elotuzumab enhances NK cell activation, directly via SLAMF7 and indirectly via CD16, and targeted killing of SLAMF7+ myeloma cells by ADCC.

Abbreviations: ADCC, antibody-dependent cell-mediated cytotoxicity; NK, natural killer.

Figure 2. Pretreating multiple myeloma cell lines with conventional therapies significantly enhanced elotuzumab-induced ADCC (* $P = 0.05$; ** $P = 0.01$). Figure adapted with permission from Tai et al [40].

Abbreviation: ADCC, antibody-dependent cell-mediated cytotoxicity.

Figure 1

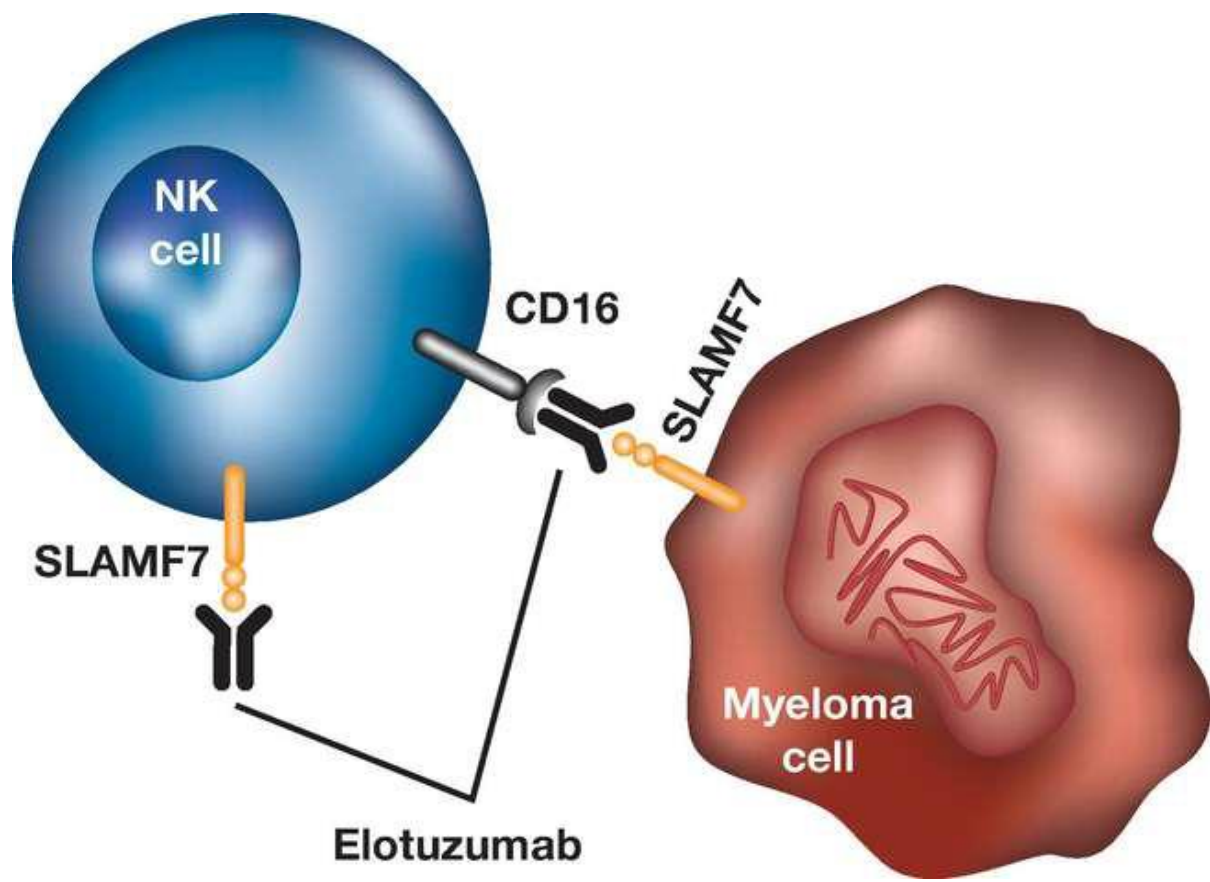


Figure 2

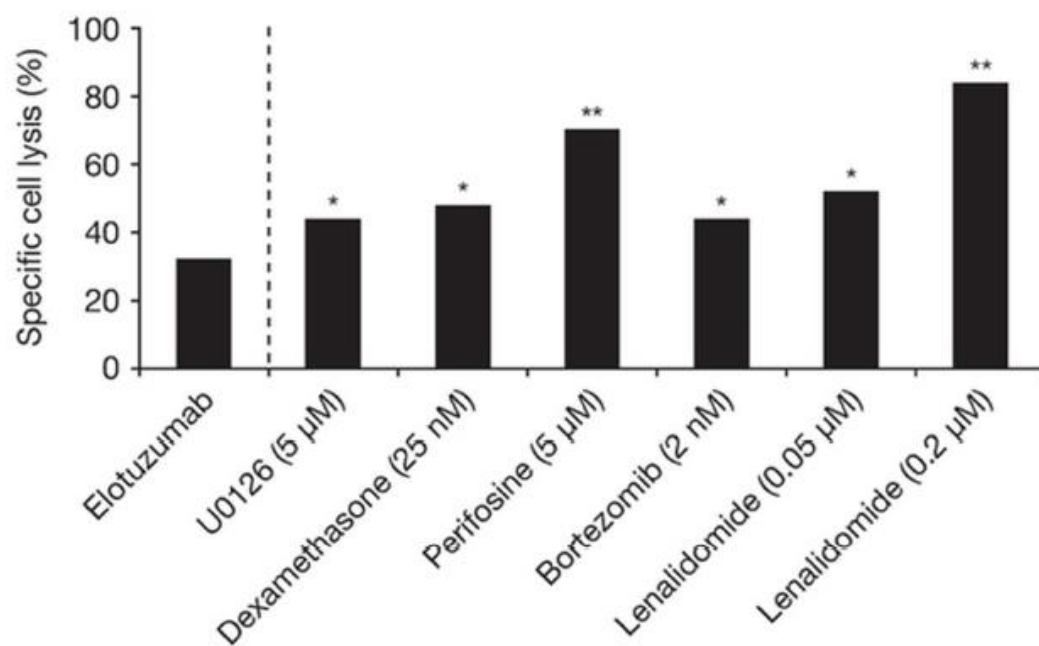


Table 1. Efficacy of elotuzumab in clinical trials

Treatment (trial ID)	Phase	Number of patients	ORR, %	Median TTP/PFS, months	Reference
Elotuzumab monotherapy (NCT00425347)	I	35	0	–	Zonder et al., 2012 [44]
Elotuzumab and bortezomib (NCT00726869)	I	28	48	9.5 ^a	Jakubowiak et al., 2012 [45]
Elotuzumab with lenalidomide and dexamethasone (NCT00742560)	IB	29	82	NR ^b	Lonial et al., 2012 [46]
Elotuzumab with lenalidomide and dexamethasone (NCT00742560)	II (20 mg/kg cohort)	37	76	25 ^b	Richardson et al., 2014 [47]
	II (10 mg/kg cohort)	36	92	32	

Abbreviations: ORR, objective response rate; PFS, progression-free survival; TTP, time to progression.

^aMedian TTP; ^bMedian PFS

Table 2. Frequent adverse events with elotuzumab in clinical trials

Treatment (trial ID)	Percentage of patients with treatment-related/emergent AEs, %	Treatment-emergent AEs, %	Serious treatment-emergent AEs, %	Reference
Elotuzumab monotherapy (NCT00425347)	Any grade: 53 Serious AEs: 18	Chills: 32 Pyrexia: 18 Flushing: 12 Chest discomfort: 9	Bradycardia: 3 Chest discomfort: 3 Chills: 3 Hypersensitivity: 3	Zonder et al., 2012 [44]
Elotuzumab and bortezomib (NCT00726869)	Any grade: 100 Grade 3/4: 79	Fatigue: 82 Anemia: 71 Diarrhea: 71 Thrombocytopenia: 68	Lymphopenia: 25 Fatigue: 14 Thrombocytopenia: 11 Neutropenia: 11	Jakubowiak et al., 2012 [45]
Elotuzumab with lenalidomide and dexamethasone (NCT00742560)	Serious AEs: 43	Diarrhea: 66 Muscle spasms: 62 Fatigue: 56 Constipation: 51 Nausea: 48 Upper RTI: 47	Neutropenia: 36 Thrombocytopenia: 21	Lonial et al., 2012 [46] Richardson et al., 2014 [47]
Elotuzumab with lenalidomide and dexamethasone (NCT00742560)	Grade ≥3	NA	Lymphopenia: 19 Neutropenia: 18 Thrombocytopenia: 16 Anemia: 14	Lonial et al., 2013 [48]

Abbreviations: AE, adverse event; NA not available; RTI, respiratory tract infection.

Table 3. Summary of completed and ongoing elotuzumab clinical trials in multiple myeloma

Trial ID	Study population	Design	Primary endpoint	Number of patients
Monotherapy trials				
NCT00425347 (Zonder et al., 2012 [44])	Relapsed/refractory multiple myeloma	Phase I dose-escalation study of elotuzumab monotherapy	Safety (MTD)	35
NCT01441973	High risk smouldering myeloma	Phase II biomarker study of elotuzumab monotherapy	Association between change in monoclonal protein and percentage of CD56 ^{dim} NK cells	40
Combination therapy trials				
NCT00726869 (Jakubowiak et al., 2012 [45])	Relapsed/refractory multiple myeloma	Phase I/II dose-escalation study of elotuzumab and bortezomib	MTD of elotuzumab	28
NCT00742560 (Richardson et al., 2014 [47])	Relapsed/refractory multiple myeloma	Phase IB/II dose-escalation study of elotuzumab with lenalidomide and dexamethasone	Phase I: MTD; phase II: ORR	102
NCT01668719 (Usmani et al., 2014 [67])	Newly diagnosed high risk multiple myeloma	Phase I/II study of optimal induction therapy of bortezomib, dexamethasone and lenalidomide with or without elotuzumab	PFS	122
NCT01393964 (Berdeja et al., 2014 [68])	Newly diagnosed or relapsed/refractory multiple myeloma	Phase IB study of elotuzumab with lenalidomide and dexamethasone in multiple	PK/PD properties of elotuzumab	26

		myeloma patients with various levels of renal function		
NCT01241292	Relapsed/refractory multiple myeloma	Phase I multiple ascending dose study of elotuzumab with lenalidomide and low-dose dexamethasone	Safety and tolerability (DLT)	20
NCT01632150 (Mateos et al., 2014 [69])	Relapsed/refractory multiple myeloma	Phase IIA single-arm study of elotuzumab with thalidomide and dexamethasone	Proportion of subjects with ≥ 1 severe (grade ≥ 3) non-hematological AE	40
NCT01478048 (Jakubowiak et al., 2012 [70])	Relapsed/refractory multiple myeloma	Phase II study of bortezomib and dexamethasone with or without elotuzumab	PFS	150
NCT02159365	Newly diagnosed or relapsed/refractory multiple myeloma	Phase II single-arm safety study of elotuzumab administered over ~60 mins with lenalidomide and dexamethasone	The percentage of patients with G3/4 infusion reactions by the end of treatment cycle 2	76
NCT01335399 (ELOQUENT-1) (Dimopoulos et al., 2012 [71])	Newly diagnosed, previously untreated multiple myeloma	Phase III trial of lenalidomide and dexamethasone with or without elotuzumab	PFS (change in expression of SLAMF7 will be examined in a biomarker sub-study)	750
NCT01239797 (ELOQUENT-2) (Lonial et al., 2012 [72])	Relapsed/refractory multiple myeloma	Phase III trial of lenalidomide and dexamethasone with or without elotuzumab	PFS	640

Abbreviations: AE, adverse event; DLT, dose limiting toxicity; MTD, maximum tolerated dose; NK, natural killer; ORR, objective response rate; PD, pharmacodynamic; PFS, progression-free survival; PK, pharmacokinetic.